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Traditional, Nontraditional, and Uremia-Related Threats for Cardiovascular Disease in Chronic Kidney Disease

Damir Rebić and Aida Hamzić-Mehmedbašić

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Abstract

As many as 40–50% of all patients suffering from chronic kidney disease (CKD) die from reasons related to cardiovascular disease (CVD). The severity of the illness is directly connected to higher mortality caused by cardiovascular factors, with the cause of the CKD not as significant for the relationship. This risk of high cardiovascular mortality and morbidity is actually so high that it surpasses the risk of the patients reaching end-stage renal disease. Within the context of CKD, CVD has certain distinct characteristics. Left ventricular hypertrophy (LVH) is commonly used as a predictor of cardiovascular (CV) mortality. The striking cardiac interstitial fibrosis, a crucial part of uremic cardiomyopathy, and nonobstructive vascular diseases are highly prevalent CV pathology in CKD patients. Traditional risk factors appear to be of less importance in the CKD population compared to the general population but have been hypothesized as uremic toxins as a risk factor of cardiorenal syndrome. In this chapter, we discuss the importance of renal function in the pathophysiology of heart failure. We also elaborate on the novel understanding of chronic kidney disease and its role in cardiovascular disease progression.

Keywords: chronic kidney disease, cardiovascular disease risk factors, traditional risk factors, nontraditional risk factors, uremia-related risk factors, cardiorenal syndrome, renocardiac syndrome

1. Introduction

Patients suffering from chronic kidney disease (CKD) have the higher risk of facing complications or mortality from causes related to cardiovascular disease (CVD) than reaching its end-stage renal disease (ESRD) [1]. In fact, 9 out of 10 patients face cardiovascular issues

and/or die due to these causes before they ever progress to ESRD [2]. A number of epidemiologic studies and research concluded that a strong relationship exists between CKD and morbidity and mortality related to CVD. Taking better care of cardiovascular (CV) risk factors during the past 10 years has led to a drop of 40% in mortality caused by coronary artery disease [3]. This, however, has not spilled over to patients suffering from CKD or those that have progression to ESRD [4, 5]. This has an effect of increasing issues caused by CVD in CKD patients, as well as highlighting further those risk factors that go alongside old age, primarily arterial hypertension, vascular calcification, dyslipidemia, oxidative stress and inflammation [6]. An aging population and increasing incidence of hypertension, diabetes mellitus, obesity and other comorbid factors are associated with an increasing incidence of cardiorenal disorders [7]. Risk factors are usually intertwined, making it difficult to separate the traditional and newly discovered risk factors, which actually have very strong ties.

2. Main body

2.1. Reverse epidemiology

Reverse epidemiology is the paradoxical observation that the well-documented associations in the general population between dyslipidemia, hypertension, obesity and poor outcomes does not exist or even may be reversed in dialysis patients. It should be mentioned that this phenomenon is not only observed in dialysis patients but also in geriatric populations and chronic heart failure (CHF). Studies have suggested that this confounded epidemiology is due to the overriding effect of malnutrition and persistent inflammation [8].

CVD in the setting of CKD has its own specific characteristics. First, despite the high incidence of accelerated atherosclerosis and high fatality following myocardial infarction (MI) in patients suffering from chronic kidney disease, a very small number of heart disease-related deaths are caused by ischemic heart disease—between 15 and 25% [9]. CVD-caused mortality is predicted by left ventricular hypertrophy (LVH), which is typically used as a forecaster. The mortality usually happens in the form of heart failure, myocardial infarction and sudden cardiac failure. Regardless of hypertension, a common cardiovascular pathology in patients with CKD is striking cardiac interstitial fibrosis, which occurs within uremic cardiomyopathy and nonobstructive vascular disease. Most common examples would be vascular stiffness, calcification and ossification [10]. These causes are predictive of negative cardiovascular events and can be used in explaining why sudden cardiac death and ischemic heart disease occur so often when there is no significant atherosclerosis. Importantly, traditional risk factors of CVD that we know are not as important in patients suffering from CKD as they are in the general population. Primarily, this is in reference to hypertension, diabetes mellitus, smoking and hyperlipidemia [9]. This can be seen through a stubbornly high CV mortality in CKD patients who control these factors. Evidence appearing right now indicates that uremic toxins and abnormal calcium-phosphate metabolism, which belong to novel CKD risk factors, directly add to the development and evolution of cardiovascular

disease. Chronic kidney disease is already by nature a progressive kind of disease, which is further augmented through these factors, which, in turn, increase the risk for the “cardio-renal syndrome”.

Also, it has been hypothesized that uremic toxins as a risk factor of cardiorenal syndrome. Despite tremendous advances in the development of dialysis technology, CV mortality is still unacceptably high in dialysis patients. Rates of all-cause mortality for dialysis patients are 8.2 times greater than the general population. After CVD has started off, the probability of survival after a five-year period reduce to 18% and 47% for patients on dialysis and following transplantation, respectively. This is quite low compared to 64% survival chance of general population. Patients in long-term dialysis must take special care of their left ventricular hypertrophy development [11] that develops even if the blood pressure level is normalized and is no longer anemic. Three-quarters of patients on dialysis for more than 10 years have left ventricular hypertrophy (LVH). Cardiac fibrosis gets worse with time in these patients but its effect are reversed after transplantation has been performed [12]. An interesting finding is the negative correlation between duration of renal replacement therapy (RRT) prior to the transplantation and the recovery of cardiac functions after a successful procedure. Dialysis performed now fails to discard a large quantity of organic matter completely, which under normal conditions be excreted by the kidneys. This is because of its high molecular size and high protein affinity [12]. Due to pathophysiological actions of this matter, these uremic compounds can add to the overall CV risk in patients with chronic renal disease. According to their physicochemical determinants, there are three groups of uremic-retention compounds: small compounds soluble in water, middle molecules and small protein-bound compounds [13]. These uremic-retention solutes with negative biological effects are called uremic toxins.

In the past few years, we have reached some understanding to their cardiovascular adverse effect, but we still need to reach conclusions regarding the mechanisms through which this occurs [13].

2.2. Pathophysiologic mechanisms

It is unclear as to what causes this high risk of cardiovascular disease in CKD patients. Uremia and ESRD-related risk factors, some of which are older age, hypertension, dyslipidemia, diabetes mellitus and LVH, are highly prevalent in CKD. However, these factors do not fully account for the extent of CVD in CKD. Several cross-sectional studies have suggested that other factors that are not included in the Framingham risk profile may play an independent and important role in promoting vascular disease in these patients. Unique risk factors related to ESRD and uremia such as hemodynamic and metabolic alterations, hyperhomocysteinemia, oxidative stress, inflammation and anemia have been identified and also likely contribute to the excess CVD risk [14]. Several mechanisms are involved in the pathophysiology of CVD in CKD interrelated and complex ways. In CKD, several clinical pathologic entities underlie CVD, including endothelial dysfunction, accelerated atherosclerosis, arteriosclerosis, and cardiomyopathy [15].

2.3. Neurohumoral activation and hemodynamic alterations

Hemodynamic changes and neurohumoral factors such as renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS) activation play an important role in the interactions between the heart and the kidneys in patients with CKD and CVD (**Figure 1**). RAAS and SNS are both key regulatory systems for the maintenance of cardiovascular and renal function. Loss of renal mass in CKD leads to the accumulation of sodium and water resulting in hypertension and fluid overload in patients with Cardiorenal syndrome (CRS). In the setting of CKD, elevated concentration of angiotensin II increases sodium retention, regulates glomerular filtration rate (GFR), potentiates the renal effects of SNS stimulation and increases release of arginine vasopressin (AVP) from the posterior pituitary gland and aldosterone from the adrenal cortex [16].

Sympathetic stimulation results in several physiologic changes that under normal circumstances serve to maintain cardiac output and vascular integrity. In the setting of heart failure, overactivity of SNS worsens cardiac performance. Sympathetic hyperactivity is present in early and advanced stages of CKD, with levels that increase with worsening renal function [17]. Overdrive of renal adrenergic receptors promotes release of renin from juxtaglomerular cells and reabsorption of sodium from tubular cells. Angiotensin II and aldosterone

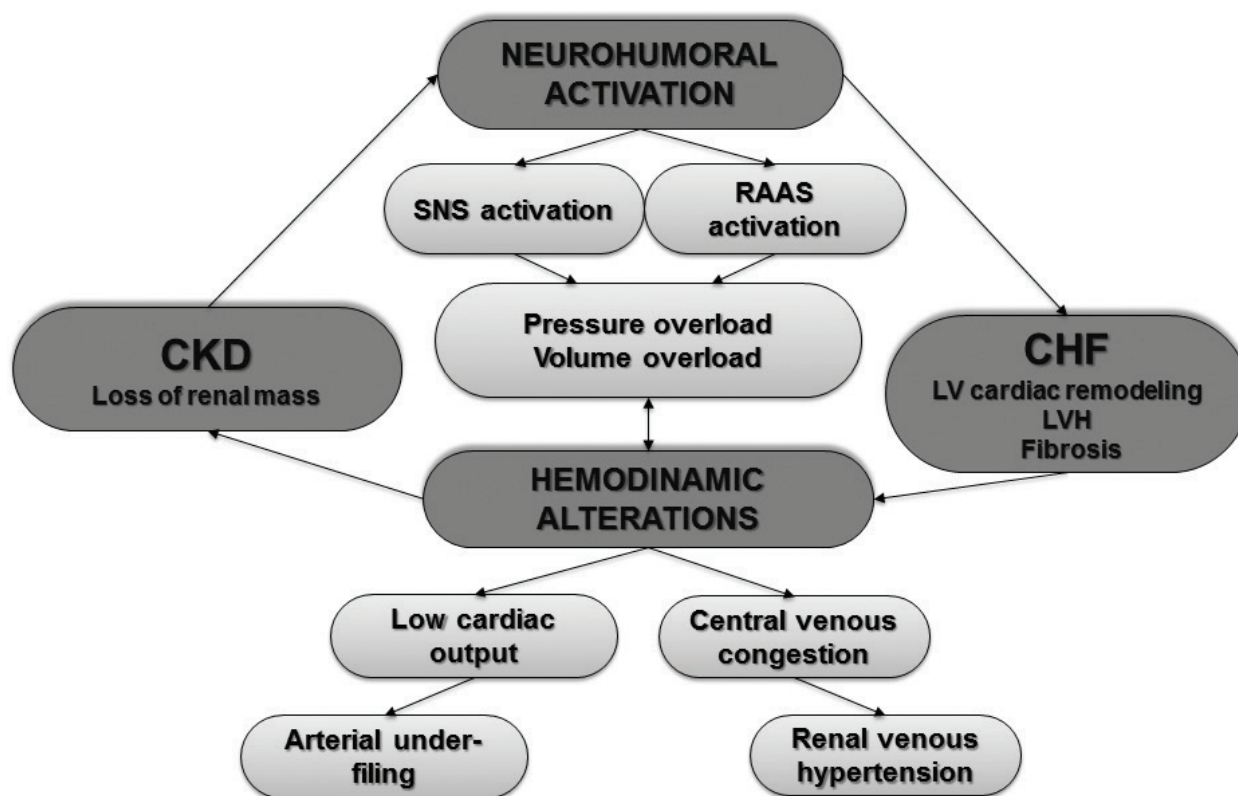


Figure 1. Neurohumoral activation and hemodynamic alterations in CKD and CHF. *Note:* CKD, chronic kidney disease; CHF, chronic heart failure; SNS, sympathetic nervous system; RAAS, renin-angiotensin-aldosterone system; LV, left ventricular; LVH, left ventricular hypertrophy.

both causes systemic arterial vasoconstriction and directly promote cardiac remodeling. AVP exerts its physiologic effects via activation of V1 and V2 receptors. Activation of V1a receptors on vascular smooth muscle cells results in vasoconstriction, while activation of V2 receptors on the collecting duct increases reabsorption of hypotonic water. Patients with CKD and CHF suffer from elevated afterload occurring after an increase in systemic vascular resistance, which arises from vasoconstriction mediated by the V1a receptor, as well as from increased preload due to water retention that occurs following the anti-diuretic effect mediated by the V2 receptor. AVP also has direct promoting effect of fibrosis and myocardial hypertrophy [18].

Volume overload occurs, due to expansion of extracellular fluid arising from aldosterone, which is responsible for the rising reabsorption of sodium and water. Ventricular filling pressures increase, caused by retention of fluids, resulting in symptoms connected with HF such as dyspnea, jugular venous distension, hepatic congestion, peripheral edema and orthopnea. Preload, or higher ventricular filling pressures, increase the workload of heart and cause dilatation of the damaged ventricle. Other conditions along with chronic kidney disease increase the cardiac output demand, leading to volume overload; chronic anemia is one among them. It is the condition where the oxygen-transporting capacity of blood has gone down. Another is when the patient has an arteriovenous fistula for the hemodialysis (HD) access, which requires some cardiac output, leaving less to systemic circulation [19].

Regulation of sodium balance is important for the maintenance of appropriate blood pressure and body fluid volume. Increased blood pressure resulting from a normal cardiac response to increasing fluid volume and pressure natriuresis and which is required for excretion of excess sodium and body fluid. Abnormal pressure natriuresis in heart failure due to low cardiac output has been described in low-flow theory. In patients with CKD who have insufficient sodium excretion because of reduced GFR due to reduced numbers of functional nephrons, there is an insufficient pressure natriuresis. Pressure natriuresis is also affected by neuro-humoral factors such as RAAS and SNS. The combination of pump failure and low cardiac output leads to vascular congestion and edema that are worsened through a nonsensical renal reaction where water and sodium retention occurs, even though extracellular volume is expanded. Vascular congestion and edema become worse, under these conditions [20].

Low cardiac output and arterial underfilling are previously thought to be main causes of impaired renal function in heart failure. However, some evidence suggests that renal venous hypertension due to venous congestion, rather than arterial underfilling, may cause renal dysfunction. Central venous congestion is clinically evident as increased jugular venous pressure and peripheral edema. Increased central venous is transmitted downstream to the capillary beds of other organ systems including the kidneys. Recent clinical trials showed the relationship between increase in central venous pressure and decrease in estimated GFR [21]. GFR is considered to decrease in response to reduction in the net filtration pressure caused by increased hydrostatic pressure in Bowman's capsule secondary to increased interstitial pressure. These factors suggest that abnormal pressure natriuresis due to decreased GFR, exacerbation of venous congestion and worsening of heart failure due to low cardiac output create a positive-feedback cycle [16].

2.4. Uremic cardiomyopathy

In the general population, pathological LVH is connected to poor survival prognosis, the development of diastolic dysfunction, arrhythmias and cardiac failure progression. A similar state is present with predialysis, as well as dialysis patients. Although the terms used to describe this condition overlap, uremic cardiomyopathy marks the influence of reduced renal function on functional cardiac capability [22]. Epidemiological studies show that the primary manifestation of uremic cardiomyopathy is LVH. Reduced renal function in different stages of arrest, combined with cardiac diseases, most often causes the development of uremic cardiomyopathy. Go et al. in a study on a large number of examinees determined that the reduction of GFR by 50%, increases the overall risk of death by five times [23]. The treatment of ESRD by kidney transplantation severely reduces the risk of cardiovascular death, but with persistence of some mortality risks. The study conducted by Zoccali et al. shows that short-term dialysis patients have a better prognosis and survival concerning cardiovascular diseases post kidney transplantation. The same authors determined that LVH is an independent factor of cardiovascular risk, connected to significant survival rate reduction [24]. LVH pathogenesis in uremic cardiomyopathy remains uncertain. Taking into account the high frequency of hypertension in patients with a difficult chronic renal disease, one of the hypotheses is that LVH occurs as a product of blood pressure encumbrance. In patients with diabetic nephropathy, blood pressure, as an independent risk factor, leads to the increase of left ventricular mass (LVM), as well as the LV mass index (LVMI). The application of blood pressure drugs, as well as dialysis treatment successfully reduces ventricular mass [25], and so, this treatment is used in normotensive patients. The application of angiotensin-converting enzyme (ACE) inhibitors reduces LVM in dialysis patients, previously normotensive. Larsen et al. have shown that left ventricular wall size is reduced in patients on intensive, continuous and daily dialysis, over the course of a year, unlike those patients who had intermittent dialysis three times a week, despite similar systolic blood pressure values. Another potential cause of uremic cardiomyopathy is volume encumbrance, which can cause the development of eccentric LVH, by increasing left ventricular end diastolic diameter (LVEDD). The reduction of interdialytic mass correlates with LVMI reduction, but LVH can persist, irrelevant of LVMI normalization. Another hypothesis on the etiology of uremic cardiomyopathy is that the accumulation of hypertrophic growth factor, connector to ESRD, initiates signal activation independent of mechanical stress, which leads to cardiac pathology progression. Several matters can modulate cardiac growth and function, which are accumulated in ESRD patients, primarily endothelin-1, parathyroid hormone (PTH), tumor necrosis factor alpha (TNF- α), leptin, interleukin1 alpha (IL-1 α) and interleukin 6 (IL-6) [26].

2.5. Left ventricular hypertrophy

The prevalence of LVH is high among patients suffering from ESRD. Structural changes appear in the early stages of kidney function damage. In prospective research, just prior to the start of RRT, 74% of patients had LVH, with a high LVMI, as an independent mortality predictor after 2 years of dialysis treatment. Up to 80% of dialysis patients have increased LVM [27]. The increase of LVM in ESRD patients can be caused by an increase of LVEDD as

a result of volume encumbrance, the increase of LV wall thickening, and the combination of characteristics of both eccentric and concentric LVH. The precise distinction of LVH between eccentric and concentric is sometimes difficult in hemodialysis patients, because of cyclical variations of extracellular fluid and humoral balance. The internal dimensions of LV are under the influence of the volume status, and the decrease of blood volume during dialysis reduces LV diameter, causing "acute" changes in the relative thickness of the left ventricular wall. In stable patients with compensated hypertrophy, the systolic function remains within normal boundaries, while diastolic charging often varies. The LVH is an adaptive response to increased heart rate. LVH is both damaging and beneficial at the same time. The benefits are tied to the number of sarcomeres and the increase of heart function capability, which allows for energy conservation. Such an effect sustains normal systolic function during the initial, compensated, or "adaptive" phase of LVH development. Continued stress gradually leads to an "inappropriate" hypertrophic response. In this phase of LVH, a loss of balance between energy consumption and production occurs in the activated myocardial cells, which eventually results in chronic energy deficiency and accelerated myocyte death [28]. The increase of extracellular matrix and collagen content makes the functional competence of heart contractions sustainable, however, at the expense of weakened diastolic charging. LVH usually occurs as a response to initiated mechanical stress. Pressure encumbrance results in the parallel addition of new sarcomeres, with a disproportionate increase in LV wall thickness and a normal ventricular diameter (concentric hypertrophy). Volume encumbrance primarily results in the addition of new sarcomeres in series, and a secondary order of new sarcomeres parallel, which again leads to the increase of LV diameter, with an increase of wall thickness (eccentric hypertrophy). The development and markings of LVH are under the influence of several factors such as age, gender and race, a co-existing disease such as diabetes, systemic disease or kidney failure [29] (**Figure 3**).

2.6. Vascular remodeling and CKD

The changes in the vascular system of uremic patients are attributed to a synergistic effect of numerous factors such as dyslipidemia, prothrombotic factors, anemia, hypertension, increased oxidative stress, hyperparathyroidism, synthesis disorder homocysteine and nitric oxide, endothelial dysfunction as well as LV remodeling, which leads to the modification of structural and functional cardiac and vascular characteristics.

Accelerated atherosclerosis and more frequent and generally higher intensity cardiovascular events go alongside CKD. Atherosclerosis is an intimal disease where vascular lesions and plaques develop. A specific morphology can be noticed in lesions in patients with CKD. They can be calcified, with media thickness. In contrast, the atherosclerotic lesions are fibro atheromatous in the general population.

In CKD, as in the general population, the accumulation of conventional risk factors initiates the atherosclerotic process. Among these risk factors, dyslipidemia is a major determinant.

More than one CKD uremia-related factor leads to renal function which is substantially reduced. Despite multiple pathobiological factors being involved, vascular disease is aggravated by the

calcification of the intimal atheromatous lesions and vascular wall media, which are representations of mineral metabolism disturbances.

Older populations suffering from CKD have a higher prevalence of occlusive atherosclerotic disease. Clinically, this is mirrored as ischemic heart disease (myocardial infarction, angina and sudden cardiac death), heart failure, peripheral and cerebrovascular vascular disease [30].

Arteriosclerosis must be taken into consideration when discussing CKD patients with CV risk. It is a process of remodeling, diffuse and nonocclusive by nature, involving the central arteries. Its determinants are an increased luminal diameter, medial calcification, destruction of the elastic lamellae, and an extracellular matrix increase. The arterial wall shows signs of stiffness due to these changes, meaning it is not as elastic. We still do not exactly know the link between this arterial stiffness and CKD. Altered mineral homeostasis is a suspect in this connection, due to the high medial calcification. In the ESRD, hyperphosphatemia, a higher level of calcium-phosphate product, hyperparathyroidism and lower 1.25-dihydroxyvitamin D levels are characteristics of mineral imbalance metabolism [31].

Diffuse nonocclusive medial calcification and increased arterial stiffnesses are the more dominant forms of vascular pathology in adolescents and young adults with CKD. These morphologic changes are associated with systolic hypertension, wide pulse pressure, LVH, coronary hypoperfusion, further renal damage, congestive heart failure and sudden death (Figure 2).

Impaired endothelial function is a characteristic of early stages of chronic kidney disease, and multiple possible causes have been identified: (1) reduced clearance of endothelial NO

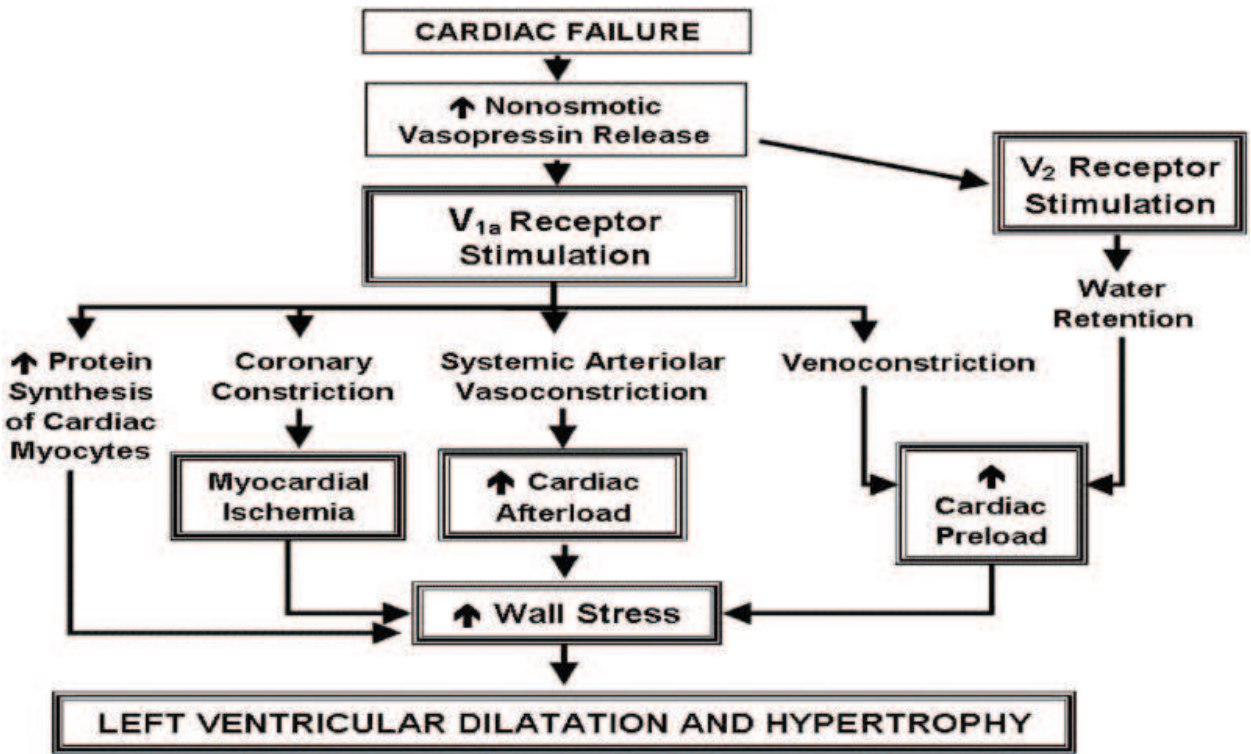


Figure 2. Mechanisms left ventricular remodeling.

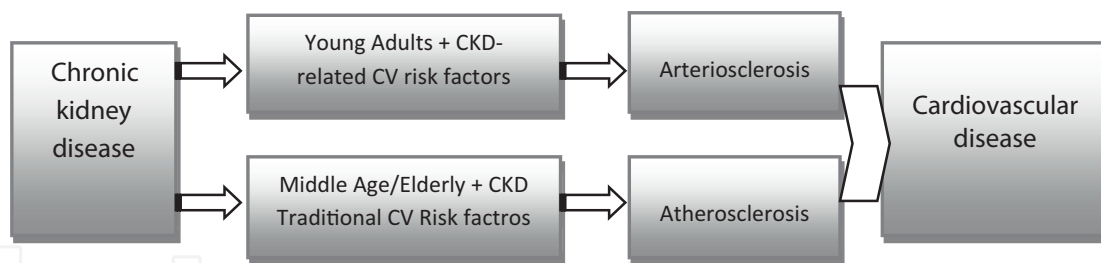


Figure 3. Pathogenesis of atherosclerosis and arteriosclerosis.

synthase (e-NOS) inhibitor asymmetric dimethylarginine (ADMA), which leads to reduced bioavailability of endothelial NO; (2) activation of angiotensin II, which induces oxidative stress; (3) high levels of homocysteine; (4) chronic inflammation; (5) dyslipidemia and (6) endothelial progenitor cell deficiency [32]. Endothelial dysfunction contributes significantly to the initiation and progression of CVD in CKD. It exacerbates arterial luminal narrowing and arterial wall stiffening by allowing development of intima-media thickening, medial hypertrophy and calcification [30].

2.7. Uremia-related CVD

A significant number of patients with uremia that are in the late stage of their renal disease show the following: (1) symptoms of myocardial ischemia without coronary artery disease by coronary angiography and (2) difficult or impossible to treat congestive heart failure. Functional and morphological characteristics of uremia are to blame for the existence of these clinical conditions [33]. As they are expected to enter ESRD, and as their kidney function is worsened, patients suffering from uremia generally have hypertension, anemia, hyperactive circulation caused by arteriovenous fistulae, increased stiffness of the arteries, and LVH and cardiac dilatation caused by overload of pressure and volume and a metabolic profile that does not fit normal characteristics. The myocardium structure is also changed due to intra-myocardial thickening of the coronary artery, reduced density of myocardial capillary and higher levels of interstitial myocardial fibrosis. These factors put together lead to cardiomyopathy. Chemical anomalies in patients suffering from CKD or ESRD, including hyperkalemia, uremia, acidosis and calcium/phosphorus dysregulation, lead to higher rates of cardiac arrhythmia [33]. Primary cardiac arrhythmias account for 50% of CV deaths in patients with ESRD. Structural heart disease secondary to CKD/ESRD such as LVH, valvular abnormalities, conduction system calcification and heart failure can independently worsen the outcome of arrhythmias in this population [34].

CVD progression in CKD a higher and burden is undoubtedly connected with the late stages of CKD. In comparison with individuals of the same gender and age from the general population, ESRD patients face 100 times higher morbidity and mortality rates. Accelerated CVD is promoted by chronic kidney disease, which is one of its most significant risk factors. The relationship is an exponential one between CKD and CVD. It is already in the first stages of kidney damage that the risk starts growing and continues all the way through to the late stage disease, where ESRD patients face 20–30 times higher risk than the general population. The

risk can be seen when eGFR levels are below 50–60 ml/min/1.73 m², and it becomes extremely high once eGFR drops <45 ml/min/1.73 m² [33].

2.8. CVD in kidney transplant recipients

Although kidney transplant recipients recover adequate renal function, CVD remains an important cause of morbidity and mortality: mortality rates are twice as high as in mortality rates are twice as high as in the general population, adjusted for age and gender. The most likely explanation is the high prevalence of conventional risk factors such as hypertension, diabetes mellitus, LVH, and dyslipidemia, as well as risk factors that do not belong to the traditional spectrum, that are connected to transplantation such as the effect of immunosuppressive medication or organ rejection. In comparison with the population in dialysis, patients that conducted a kidney transplant have a lower rate of CVD mortality. This is most likely caused by the removal of kidney-specific risk factors following the transplantation [35].

3. Traditional risk factors

Hypertension, smoking, hyperlipidemia, obesity and diabetes are all risk factors which are connected to CVD in general populations, but also in PD patients, and are categorized into so-called traditional risk factors.

3.1. Age and gender

Male gender is another well-known risk factor for CVD in the general population, and the frequency of acute myocardial infarction is as much as 2.5 times higher than in the female population suffering from CKD, adjusted for age. However, due to menopause caused by age or comorbidity, the senior female population will also be at higher risk of CVD. Research has shown that about 70% of women on hemodialysis (HD) were menopausal before or after starting RRT, and the incidence of Acute Myocardial Infarction (AMI) was 3–5 times higher in female patients suffering from chronic kidney disease, compared to the age-adjusted general population [36, 37].

3.2. Tobacco smoking

Smoking is not only a risk factor for the development of CVD but is also connected to the risk of developing CKD, defined as the reduction GFR at <45 ml/min/1.73 m². In a large study from Norway, long-term smoking of over 20 cigarettes a day is connected to 1.52 times increased the relative risk of CKD occurrence [38]. However, it is relatively unknown whether smoking increases the risk of CV death in dialysis patients. A small study on diabetic dialysis patients found no effects of smoking on the risk of CV death, although a series of studies showed that smoking, or a history of smoking, is an independent risk factor for increased morbidity and mortality [39]. These apparent differences can be framed through the presence of other risk factors in some populations, which can supersede the effects of smoking in various multivariable analyses.

3.3. Diabetes mellitus

North-American registry data show that the number of diabetic patients annually admitted to RRT more than doubled from 1995 to 2000. Diabetes mellitus has become the single most important cause of ESRD. Renal replacement therapy continues showing unsatisfactory results for diabetic patients, as survival rates are low. Compared to dialysis patients with other underlying kidney conditions, those with diabetes have the lowest chance of survival. The main cause of death is coronary heart disease—myocardial infarction (MI), angina, history of bypass surgery, PTCA and pathology on coronary angiography. Cardiovascular issues, primarily coronary atheroma, add up before the diabetic patient enters renal replacement therapy programs. Therefore, it is crucial to improving care for the patient with diabetes before he enters the end-stage of the disease. Diabetic patients with underlying CKD face an increased cardiac risk after developing acute MI, which is mirrored through atrial and ventricular arrhythmia, atrioventricular (AV) block, asystole, pulmonary congestion and cardiogenic shock [40].

3.4. Arterial hypertension

Arterial hypertension is very common in CKD patients and is connected to increased risk of CV death [41]. Hypertension is often present in dialysis patients. According to the results of an Italian multicentric study, 88% of 504 patients treated with RRT suffer from arterial hypertension, with anti-hypertensive therapy included. Arterial hypertension in dialysis patients is usually connected to volume encumbrance. In a report by the UK renal registry in 2008, it is stated that in a larger number of patients treated with HD the targeted blood pressure was achieved, as opposed to peritoneal dialysis (PD) patients (45–33%) [42]. However, unlike the general population of dialysis-treated patients, the connection between high blood pressure and mortality is not so pronounced. Hypertension strongly correlates with LVH, which is often found in CKD. Almost 70% of patients at the beginning of dialysis therapy suffer from an echocardiography recognizable LVH. According to research done by Coen et al., LVH is more potent in long-term dialysis patients than in HD patients, most likely because of inadequate volume control [43].

Low blood pressure has a negative effect on the rates of survival of dialysis patients. However, hypertension is used as a predictor of mortality in patients with CKD before or at the initiation of dialysis. To be able to comprehend this paradox, a separation of blood pressure must be made into systolic, diastolic, mean arterial pressure (MAP) and pulse pressure. Isolated systolic hypertension combined with a high pulse pressure is the most common anomaly regarding blood pressure in patients on dialysis. This occurs due to medial sclerosis of arteries with secondary arterial stiffening. This, in turn, leads to higher pulse-wave velocity, creating an increased peak systolic pressure thanks to a pulse wave reflected too early. LV dysfunction and congestive heart failure occur as a result. A consequence, afterward, could be a lower MAP and diastolic pressure, combined with high CVD risk. Altogether, this points to a U-shaped relationship between blood pressure and mortality: isolated systolic hypertension and increased pulse pressure probably point to high risk, in the long-run, in dialysis patients, whereas low mean and diastolic blood pressure predict a high change of early death. The danger that is not obvious, when it comes to hypertension, is that a large percentage of CKD patients are “nondippers”, that is, do not have their blood pressure levels drop during the night. Sleep apnea has been shown to be a condition in CKD which has not attracted as

much attention as necessary, considering it is associated with no dipping blood pressure, SNS activation and increased CVD risk [44].

3.5. Atherosclerosis

It has been proven that arterial rigidity, which is usually estimated by pulse-wave velocity on the aorta, the quantity of common carotid artery (CCA) intima-media thickness (IMT), and also by peak systolic velocity in the systole on the CCA, is a useful predictor of CV morbidity and mortality in the general population, and as such, in patients suffering from CKD.

Zoccali et al. [38], through their research, have determined that in a large group of patients suffering from CKD, the rigidity of large arteries was independently connected with age, blood pressure, as well as other risk factors for the development of CVD. The presence of vascular calcifications has shown itself to be one of the most prominent factors connected to arterial rigidity. However, relevant studies in dialysis patients are relatively small and have numerous limitations [45].

3.6. Obesity

Obesity is a risk factor for the development of CV diseases in the general population but is also connected to an increased risk factor for the development of CKD. The results of studies performed on dialysis patients have not been consistent about the influence of obesity on survival rates. The results of some studies showed that obesity is connected to better survival rates, while other studies have discovered that there is a connection between obesity and increased mortality risk. A prospective, time limited analysis in 688 dialysis patients showed that only those with a BMI <18.5 have an increased risk of CV death. High BMI had no protective effective but was also not connected to reduced survival risk [46].

3.7. Dyslipidemia

Dyslipidemia is known as a traditional risk factor for CVD in the general population, as well as in dialysis patients. Several observational studies have shown that the values of cholesterol and low-density lipoprotein (LDL) are among the most significant independent CV morbidity and mortality factors. Patients with damaged renal function suffer from significant changes in lipoprotein metabolism, which has a precise role in atherosclerotic pathogenesis. This is still controversial [47]. Renal dyslipidemia is characterized by an atherogenic apolipoprotein profile. This means there are lower levels of apolipoprotein A (apoA)-containing lipoproteins and higher levels of apoB-containing lipoproteins. CKD, as a progressive disease, is connected with high levels of apoCIII. Whereas total serum cholesterol levels, in general, are normal, or even low, high-density lipoprotein (HDL)-cholesterol is reduced; and low-density lipoprotein (LDL), intermediate-density lipoprotein (IDL), very low-density lipoprotein (VLDL)-cholesterol, plasma triglycerides, and lipoprotein(a) (Lp(a)) levels are increased. Compared to HD patients, patients treated with PD more often have both hypercholesterolemia and hypertriglyceridemia. Elevated Lp(a) levels have been reported to be associated with increased CVD mortality both in HD and PD patients. Two randomized controlled trials showed no benefit of statin treatment in dialysis patients [48].

3.8. Insulin resistance (IR)

A number of issues found in metabolic syndrome patients such as insulin resistance (IR), can be found in chronic kidney disease as well, a so-called uremic-metabolic syndrome. The etiology of resistance to insulin in CKD is multifactorial, with factors such as fat accumulation, lack of vitamin D, metabolic acidosis, inflammation, and uremic toxins accumulation all contributing. These factors create adverse changes in the pathway for the insulin receptor signal. Available data shows that IR is present in CKD patients starting from the early stages of renal failure. The potential of IR to promote blood vessel damage, regardless of the coexistence of other vascular risk factors, is large [49]. In several studies, the role of IR in patients on dialysis was analyzed, and a connection between IR and a disturbed fatty acid metabolism has been discovered, which further contributed to left ventricular dysfunction. Also, more and more evidence points to the fact that the application of ACE inhibitors (ACEIs) can modulate IR. In PD, IR of the tissue can be worsened by the intake of glucose through dialysis solutions. However, these studies are controversial as well: in patients on cyclical PD, IR is greater than HD patients, while in PD patients, IR is normalized, similar to HD patients. By using icodextrin dialysis solutions, insulin levels in serum could potentially be reduced, and insulin sensitivity increased [50].

4. Nontraditional and/or uremia-specific risk factors

A known risk factor for the genesis of CV disease is $\text{GFR} < 60 \text{ ml/min/1.73 m}^2$. A further drop in GFR values, below $45 \text{ ml/min/1.73 m}^2$, increases the risk of CV death. Potential factors tied to CKD and uremia, as well as the development of CV morbidity, includes inflammation, malnutrition, endothelial dysfunction, oxidative stress, vascular calcifications, vitamin D deficiency and hyperhomocysteinemia [51].

4.1. Renal failure per se

Newly acquired evidence points to a strong, independent relationship between low eGFR and mortality risk, CV events and hospitalization [52]. The mechanisms behind the process of progressive renal function deterioration's acceleration of the atherogenic process are not well known. However, the presence and severity of multiple novel CKD risk factors, including inflammation, oxidative stress, vascular calcification and accumulation of advanced glycation end products (AGEs) increases. Many other accumulating solutes for uremic retention, for example, ADMA, guanidine, homocysteine, indoxyl sulfate and p-cresol, could have a pro-atherogenic effect. Kidneys may also produce substances like renase which should control and limit CVD, but a renal function deterioration leads to vascular disease through separate mechanisms and not retention.

4.2. Inflammation

Chronic inflammation is characterized by the persistent effect of a causative stimulus, destroying cells and tissue and having a deteriorating effect on the body. In later stages of CKD, the systemic concentrations of both pro- and anti-inflammatory cytokines are significantly higher

as production has increased, coupled with decreased renal clearance. Aside from this, there are plenty of dialysis-related issues (such as membrane biocompatibility and thrombosed AV fistula) and nondialysis factors (e.g. infection, comorbidity, poor oral health, failed kidney transplants, genetic factors, diet) that may contribute to a continuous inflammation.

Inflammation, the effects of local inflammatory stimuli such as oxidation products, end advanced glycosylation products and chronic infective processes modify blood vessels in the sense of atherosclerosis development. These changes benefit proatherogenic adhesion molecule production, for example, intercellular adhesion molecule1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1), growth factor, as well as chemokine (such as IL-6, long pentraxin 3 (PTX3), S-albumin, TNF and white blood cell count). Such inflammatory intermediates encourage the synthesis of acute phase proteins such as C-reactive protein (CRP), reduction of albumin synthesis in the liver of dialysis-treated patients [53], which leads to endothelial dysfunction, which is usually defined as reduced vasodilatation capability, which again creates early atherosclerosis occurrence predisposition. However, the question, whether inflammation is a reflection of vascular damage, or actually supports factors that cause vascular injury, remains unanswered. The precise link between inflammation, endothelial dysfunction, oxidative stress, CVD and mortality in dialysis patients remains unknown. In a prospective study of dialysis patients, CRP level of >6 mg/L was an independent predictive mark of possible myocardial infarction. Aside from that, the proinflammatory IL-6 mark is increased in ESRD patients but is also an independent mortality predictor in patients on dialysis [54].

However, as many features are known to mediate atherosclerosis such as endothelial dysfunction, vascular calcification, IR, and increased oxidative stress, all are more or less associated with inflammation biomarkers, the association between chronic inflammation and CVD may also be indirect.

4.3. Endothelial dysfunction

In dialysis patients, endothelial function is reduced, the same as in hemodialysis patients, most likely because of a reduced bioavailability of NO. In a study conducted in 2009, flow-mediated vasodilatation is significantly lower in PD patients than in the healthy population, which negatively correlates with inflammation markers such as CRP or IL-6 [55]. There is evidence that suggests that the endogenous inhibitor of NO, ADMA, has a significant role in the origin and occurrence of CVD and mortality in dialysis patients. NO deficit and ADMA accumulation promote endothelial dysfunction, vasoconstriction, and arterial thrombosis. The remaining factors of endothelial dysfunction such as soluble adhesive molecules are predictors of all causes of CV in ESRD patients. The levels of VCAM-1 negatively correlate with LVH in patients undergoing RRT.

Evidence from newer studies shows that detached circulating endothelial cells (CEC) are suitable markers for endothelial damage [56]. They can be used for predicting purposes in order to prevent future CV events in HD patients. As a feedback to ischemic insult and cytokine stimulation, endothelial progenitor cells (EPC) are mobilized from the bone marrow to act as “repair” cells in response to the endothelial injury. As to reduced numbers of and/or a

functional impairment of EPC due to inflammation and/or toxic effects of retained uremic solutes, there seems to be a disparity between EPC and CEC, which could eventually cause endothelial dysfunction in CKD patients.

4.4. Malnutrition and protein-energy wasting (PEW)

A marked connection between malnutrition, increased levels of CRP and atherosclerosis is well known, although the precise mechanisms of their synergistic effects on the organism are not known. This relationship was first described by Stenvinkel et al. in a study on CKD patients [57]. Patients with CRP levels >10 mg/L have significantly lesser values of serum albumin and a higher prevalence of atherosclerosis than patients with a lower CKD level. The combination of malnutrition, inflammation and atherosclerosis presence has been described by Stenvinkel as MIA (Malnutrition Inflammation Atherosclerosis) syndrome. A 2008 study has shown that MIA syndrome is connected to increased mortality risks [58]. In a Korean study, comorbidity cardiovascular diseases were present in 78% of patients on dialysis with signs of malnutrition. These patients have a 3.3 times greater risk of mortality than patients suffering from malnutrition with no comorbidity conditions [59]. Taking malnutrition, protein deficits, and inflammation into account, the recommendation for the description of this entity in CKD patients is protein-energy wasting (PEW). PEW is characterized by reduced protein and initiation energy accumulation. Several studies have shown that there are two types of malnutrition: the first is connected to poor food intake, and the second to inflammation and present comorbidity. Low levels of serum albumin can only be found in the second type of malnutrition, but the exact contribution of malnutrition or inflammation in the development of risk of CV mortality in dialysis patients remains uncertain [58]. A large number of studies have dealt in hypoalbuminemia and the outcome of treating patients on dialysis. It has been determined that serum albumin levels below 40 g/L are combined with 4–20 times increased mortality. In addition, 45% of PD patients die during the first year of dialysis treatment in cases where albumin levels drop below 25 g/L. A CANUSA study has shown an 8% survival rate increase in cases of serum albumin growth of only 1% [60].

4.5. Oxidative stress

Oxidative stress is defined as the damage of tissue which stems from the disturbed balance between excessive oxidation compound production and insufficient anti-oxidant defensive function. CKD patients have a deficiency in the anti-oxidant defensive mechanism (because of e.g., reduced vitamin levels, or hypoalbuminemia) and increased pro-oxidant compound activity (e.g. accumulation of solvent materials such as AGEs and β 2-microglobulin). Oxidative stress leads to the production of free radicals, highly reactive compounds that can oxidize proteins lipids and nucleic acids. High concentrations of these molecules are present in CKD patients. Oxidation products of proteins and oxidized DNA have been discovered in leukocytes with residual renal function (RRF). The underlying connection between increased levels of oxidation stress and the risk of CV death in ESRD patients is still unknown, even though the results of several prospective studies point to the conclusion that oxidation stress can be a risk factor for CV morbidity and mortality in ESRD patients [14]. Four pathways of

oxidative stress exist in CKD (carbonyl stress, nitrosative stress, chlorinated stress and classical oxidative stress). Evidence suggests that oxidative stress plays a major role. The relation between accumulation of AGE and the cardiovascular disease's outcome is not as transparent and obvious. Studies focusing on Chronic Myelogenous Leukemia (CML) and pentosidine found no significant effect on mortality. However, one study pointed to the conclusion that skin autofluorescence predicted death in HD patients [61].

One of the most important toxins connected to the uremic environment and connected to oxidative stress and inflammation stage and the presence of inflammation biomarkers is β 2-microglobulin. Increased levels of β 2-microglobulin in plasma are a known marker of chronic renal function failure and are among the most important toxins tied to uremia. In PD patients, the level of β 2-microglobulin is primarily tied to amyloidosis. In recent times it has been suggested that β 2-microglobulin could be a new biomarker of peripheral arterial disease and an independent predictor of aortic rigidity in the atherosclerotic process, in both the general population and ESRD patients [62]. Additionally, increased levels of β 2-microglobulin present a new marker for differentiating the levels of acute cardiac arrest creation risk in patients with creatinine levels $\leq 265 \mu\text{mol/L}$ [54]. All of these results point to an important role of β 2-microglobulin in CV risk prediction in dialysis patients.

4.6. Hyperparathyroidism

In ESRD patients, the ability of the diseased kidney to produce 1.25-dihydroxycalciferol is reduced, which significantly contributes to the development of osteodystrophy, secondary hyperparathyroidism and the disturbed metabolism of divalent ions. PTH is considered a potent uremic toxin that harmfully affects myocardial cells. The improvement of left ventricular dysfunction after parathyroidectomy in uremic patients with increased PTH points to a connection between left ventricular function and hyperparathyroidism. All this confirms the assumption about the role of parathormone as a risk factor in the development of uremic cardiomyopathy. Significant research results point to the conclusion that a small level of vitamin D is connected to CVD in the general population, and that a greater concentration of that vitamin can have a positive influence on survival. Similar results were discovered in predialysis patients. Wang et al. have determined that low concentrations of serum 25-hydroxyvitamin D in dialysis patients are connected to increased risk of fatal or nonfatal CV incidents. It seems that the effects of vitamin D on the CV system are connected to residual renal function, LVH and cardiac dysfunction [54].

4.7. Cardiovascular calcification

The arterial media, atherosclerotic plaques and heart valves are affected through this cardiovascular process. One of the main signs of medial calcification is arterial stiffness, which is shown clinically through an increased pulse pressure. The pathophysiological role of plaque calcification is less clear, as it is mostly soft plaques, which rupture and cause AMI. It is now evident that the burden caused by atherosclerotic calcification is a suitable risk marker for cardiovascular events. In patients in dialysis, valvular calcification leads to a developing stenosis and morbidity that goes with it, after targeting and affecting the aortic and mitral valves [63].

In the general population, coronary artery calcification is infrequently observed in younger age groups. It is a phenomenon that increases with age, and the majority of people affected by vascular calcification are >65 years. In ESRD patients, on the other hand, extensive vascular calcification can be commonly observed in much younger age groups as well. The calcification process frequently starts before the initiation of dialysis treatment. The prevalence and extent of vascular calcification, arterial media calcification and arterial stiffness have recently been shown to be strong predictors of CVD and all-cause mortality in dialysis patients.

Besides diabetes mellitus, CV calcification can, with the presence of uremia, be caused by abnormal calcium and phosphate metabolism and an enduring inflammation as it may by several mechanisms mediate untimely atherosclerosis and premature CVD.

Fetuin-A, an important inhibitor of vascular calcification, is down-regulated during the inflammation process, and low levels are linked to poor survival in dialysis patients. However, fetuin-A is certainly not the only modifier of extraosseous calcification. Phosphate, calcium and some proinflammatory mediators have the capacity to induce osteogenic differentiation, which is a transition of vascular smooth muscle cells toward osteoblast behavior. A system of calcification inhibitors (and inducers) is of major importance, as the extracellular calcium and phosphate environment must be formally considered as being “supersaturated” regarding the chemical solubility product of these ions in an aqueous solution. Among them, leptin, matrix GLA protein, TNF- α , pyrophosphates, bone morphogenetic proteins and osteoprotegerin, may be related to a process of accelerated vascular calcification in ESRD [64].

4.8. Hyperhomocysteinemia

Homocysteine (Hcy) is a nonprotein sulfur-containing amino acid that has attracted considerable interest by vascular researchers, as it may by several mechanisms mediate premature atherosclerosis and CVD. The prevalence of hyperhomocysteinemia in patients with advanced CKD is >90%. In contrast to the well-documented association between total Hcy (tHcy) and vascular disease in the general population, the relationship between tHcy and CVD is not that clear and strong assuming renal function is reduced, with studies and reports demonstrating low levels of tHcy in patients with chronic kidney disease with CVD [13]. Although there are several reasons that may explain this paradoxical relationship, one of the most significant relationships is the strong association between tHcy and hypoalbuminemia, PEW and inflammation. S-albumin and tHcy have an established strong positive correlation, and hypoalbuminemia is an established predictor of adverse outcomes that this relationship may confound the impact of tHcy on vascular disease [65].

4.9. Autonomic dysfunction

Decreased baroreflex sensitivity is significant for CKD and one of its main attributes, which can, together with inflammation and wasting, lead to an increased risk of sudden death. Increased sympathetic nerve activity can be seen in CKD patients quite frequently, and it is a predictor of an adverse result [66]. Sympathetic overactivity is probably partial due to sleep apnea, which is considered a contributor to the condition in patients with moderate and severe-stage CKD.

4.10. Anemia

In ESRD, the condition causes LVH and LV dilatation. Normalizing hemoglobin has not shown any CV outcome improvement, despite a partial correction of anemia using erythropoietin causing a regression in LVH. The appropriate target hematocrit to minimize LVH or other CVD has not been defined. However, briefly summarizing guideline recommendations favors target hemoglobin of about 11 g/dl [66].

4.11. Hormonal disorder

The loss of kidney function and the altered metabolic milieu in CKD affects hormone secretion and response of target tissues, causing a number of endocrine dysfunctions that may affect both PEW prevalence and future CVD risk. Changes in the GH-IGF-1 axis lead to many important CKD complications such as growth retardation, PEW, atherosclerosis and disease progression. Other common hormonal disturbances in chronic kidney disease are subclinical hypothyroidism and the low-T3 syndrome, which occurs in one-fifth of CKD patients. However, chance of CV events increases in the general population with thyroid changes, and thyroid production is substantially reduced by inflammation. Therefore, the hypothesis exists saying these factors create a connection between stress caused by inflammation and a negative cardiovascular event in CKD patients [66]. Finally, during the chronic kidney disease, the sex hormone profile does not stay the same. In as many as 50–70% of males in ESRD, male hypogonadism occurs. Testosterone decline occurs for multiple reasons such as low synthesis of muscle protein and hemoglobin, as well as atherosclerosis development and arterial vasoconstriction and/or hardening. This relationship between male hypogonadism and increased risk of death caused by CV factors in dialysis patients has been brought to attention, which will hopefully put some focus on this issue. New studies conducted on nonCKD patients using low testosterone dosage showed satisfactory outcomes such as muscle gain and improved metabolism (no studies have been conducted regarding interventions targeting the adverse outcomes of CV) [67].

4.12. Residual renal function (RRF)

The residual renal function is important for dialysis patients because it contributes to total daily clearance of 20% or more. It is thought that a dialysis patient has preserved RRF if his clearance of creatinine is greater than 1.5 mL/min. In PD and HD patients, RRF is connected to all causes of mortality, and so it is connected with the risk of CV death. The vital role of RRF in the survival of PD patients was determined in large prospective studies such as the CANUSA and ADEMEX studies. In the ADEMEX study, by a prospective, randomized examination of 965 dialysis patients with a weekly diuresis of 10 L/m², a relative mortality risk drop of 11% was noted [68]. These results were also confirmed by the NECOSAD study, where the rate of reduction of RRF was a stronger predictor of mortality and technical insufficiency of long-term PD treatment, in relation to basic RRF [58].

4.13. Volume overload and ultrafiltration insufficiency

Ultrafiltration insufficiency occurs in around a third of dialysis patients and can lead to arterial hypertension and volume encumbrance. Volume overload promoted the development

of LVH and leads to increased serum concentrations of natriuretic peptide, because of their increased myocardial production. These peptides are used as a prognostic marker for the general mortality of ESRD patients [69].

The connection between the lack of peritoneal ultrafiltration and mortality has been proven in anuric patients. When fluid intake is not adjusted to peritoneal ultrafiltration, the patient will develop volume overload, which increases the risk of CVD.

4.14. Genetic and epigenetic factors

Genetic factors can influence the appearance and frequency of vascular complications in dialysis patients. Thus, polymorphism of a single nucleotide in the IL-6 gene is connected to increased levels of IL-6 in plasma, and comorbidity in HD patients, greater diastolic pressure values and left ventricular mass [70]. Polymorphism of the enzyme, which transforms angiotensin I to angiotensin II, can determine the degree of the function of recombined human erythropoietin in PD patients, which presents a significant prescreening for the assessment of erythropoietin resistance. Polymorphism on the human receptor of vitamin D is combined with an increased risk of the development of hypercalcemia, modulation of NO activity via the polymorphism of endothelial NOS, as well as functionally relevant polymorphism of the IL-6, which together can have a significant effect on basic peritoneal permeability [71]. In the future, research in this field could enable a more precise approach for the identification of risk groups of patients treated by PD, and the development of personalized treatment strategies.

A new approach in the research of atherosclerosis focuses on the role of epigenetics, which change studies in gene expression that are not coded in the DNA sequence itself but are instead a consequence of post-translatory changes in the DNA-protein. These epigenetic changes can be lost in several sequential cellular generations. Changes in the genome methylation of DNA have important regulatory functions in normal and pathological cellular processes. A persistent inflammatory reaction is most likely connected to DNA hypermethylation [72]. Further research is necessary to determine whether epigenetic DNA changes are connected to accelerated atherosclerosis in uremia.

5. Chronic cardiorenal and renocardiac syndrome interaction

The interplay between cardiac and renal disease is complex and the term CRS has been introduced recently as an attempt to describe the close interaction between CV and renal systems, especially in the chronic disease settings. Division of CRS into five categories is proposed by Ronco et al. [73]. This classification is based on etiologic and chronologic factors [74]. The temporal relationship between the heart and kidney disease as well as the coexistence of CVD and CKD represent important aspects of chronic cardiorenal and renocardiac syndromes definition. CRS type 2, or chronic cardiorenal syndrome, is characterized by chronic abnormalities in cardiac function leading to kidney injury or dysfunction. CHF causally underlies the occurrence and progression of CKD [75]. CRS type 4, or chronic renocardiac syndrome, has been defined as “chronic abnormalities in renal function leading to cardiac disease” and recognizes the extreme burden of CVD in patients with CKD such as chronic glomerular disease and autosomal dominant polycystic kidney disease (ADPKD). This is the condition where

primary CKD contributes a reduction in cardiac function such as cardiac remodeling, left ventricular diastolic dysfunction or hypertrophy, and/or an increased risk for CV events such as MI, heart failure or stroke [76].

Coexistence of the chronic heart and kidney disease was clearly described in large observational studies. However, this type of data cannot establish whether the primary process is the kidney disease (CRS type 4) or the heart disease (CRS type 2). For these situations, it has been suggested to use term CRS “type 2/4”. For example, large database studies have shown the prevalence of CKD of 26–63% in the population of CHF patients. Likewise, retrospective and/or secondary post hoc analyses from large clinical registries have evaluated the CV event rates and outcomes in selected CKD-specific populations [77]. The severity of CKD in those studies ranged from near normal kidney function to End stage kidney disease (ESKD). Furthermore, in a secondary analysis of the HEMO Study, cardiac disease was found in 80% of ESKD patients at enrollment [78]. During 12 months follow-up, 39.8% patients had cardiac-related hospitalizations with angina and acute myocardial infarction accounting for 42.7% of these hospitalizations. There were 39.4% of cardiac deaths. Baseline cardiac disease was highly predictive of cardiac-related death during follow-up (relative risk 2.57). Moreover, other authors have suggested that chronic maintenance hemodialysis induces repetitive myocardial injury and can accelerate systolic dysfunction [79].

6. Biomarkers of adverse cardiovascular events in CKD patients

Biomarkers must be determined in situations where we have renal and cardiac issues and dysfunctions, as it is crucial to know if any functional and structural damage occurred in the beginning stages of the disease. They are then used to separate the patients according to the risk level by considering established renal and cardiac parameters, in order to establish individual treatment and prognosis. These biomarkers may help with early diagnosis, prognosis, treatment and monitoring of CRS. There can be any measurable parameter, like components of serum or urine. In patients with CRS, a group of multiple biomarkers, rather than a single test, may improve diagnosis and better define prognosis [80].

Recent studies have evaluated the utility of biomarkers in the assessment of the CV risk in CKD population. Several cardiac biomarkers such as natriuretic peptides, troponins, CRP, homocysteine, plasminogen activator inhibitor 1 (PAI-1), ADMA, adiponectin (APN) and AGEs have been demonstrated to correlate with CV outcomes in CKD patients. Renal biomarkers such as cystatin C, neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), N-acetyl-beta-D-glucosaminidase (NAG), fibroblast growth factor-23 (FGF23), matrix metalloproteinases (MMPs) and interleukin-18 (IL-18) have been recently found to be diagnostic and prognostic markers of CV outcomes in CKD (**Table 1**) [81].

6.1. Cardiac biomarkers

The natriuretic peptides are family of hormones that share a common 17 amino acid ring structure and have actions targeted to protect the CV system from the effects of volume overload.

Cardiac biomarkers	Renal biomarkers
Natriuretic peptides	Cystatin C
Troponins	Neutrophil gelatinase-associated lipocalin (NGAL)
C-reactive protein (CRP)	N-acetyl-beta-D-glucosaminidase (NAG)
Homocysteine	Kidney injury molecule-1 (KIM-1)
Plasminogen activator inhibitor 1(PAI-1)	Interleukin-18 (IL-18)
Asymmetric dimethylarginine (ADMA)	Fibroblast growth factor-23 (FGF23)
Adiponectin (APN)	Matrix metalloproteinases (MMPs)
Advanced glycation end products (AGEs)	

Table 1. Biomarkers of adverse cardiovascular events in chronic kidney disease.

B-type natriuretic peptide (BNP) produced by ventricular myocardium in response to ventricular stretching, and its inactive fragment N-terminal proBNP (NT-proBNP) are well-known diagnostic and prognostic markers in patients with heart failure. BNP and NT-proBNP are also useful markers of adverse CV events and overall mortality in CKD patients. They correlate with severity of heart failure and left ventricular dysfunction and can be used in guiding the management of heart failure in CKD patients. Some evidence suggests that NT-proBNP and high-sensitivity CRP (hs-CRP) are independent predictors of overall mortality in a nondialysis CKD population and their role in risk stratification can be useful in this specific patient population [82]. Similar results were found in the dialysis-dependent ESKD patients. High levels of NT-proBNP and cardiac troponin T showed to be strongly associated with adverse CV morbidity and mortality in HD patients [83]. In chronic PD patients, NT-pro-BNP is prognostic marker of congestive heart failure, mortality or combined end point including death and other adverse CV outcomes [84].

Plasminogen activator inhibitor 1 (PAI-1), a specific inhibitor of tissue-type and urokinase-type plasminogen activators (t-PA and u-PA), plays a critical role in regulating the fibrinolysis. PAI-1 is classified as an endothelial dysfunction marker. The activated or injured endothelial cells synthesize higher rates of PAI-1 and endothelial dysfunction was recognized as an initial event of atherosclerosis. Elevated PAI-1 levels are associated with increased CV risk in the general population. Plasma levels of PAI-1 are also associated with the occurrence of a first AMI in a population with high prevalence of coronary heart disease. In addition, high plasma PAI-1 concentration was found to be independent predictor of CV in patients ongoing PD [85].

Adiponectin (APN) is a protein secreted by adipocytes with activities focusing on anti-inflammatory and anti-atherogenic goals. It also increases the body's insulin sensitivity. The way it assumed its functions are by suppressing proinflammatory cytokines such as TNF- α and IL-6 from being released and promoting the release of anti-inflammatory cytokines such as IL-10, as well as through increasing sensitivity to insulin. Through these roles, it controls anti-atherosclerotic activities. Low levels of APN can be seen in obese patients, those with metabolic syndrome, diabetes mellitus, coronary artery disease and essential hypertension. On the other hand, APN plasma levels are three times higher than regular levels in patients with

CKD, probably due to catabolism or reduced clearance. Some observational studies linked APN to adverse CV outcomes in patients with CKD. Low plasma APN levels were predictive of CV events among nondiabetic patients with mild to moderate CKD. Furthermore, low APN levels were found among the dialysis patients who developed CV complications [86].

6.2. Renal biomarkers

Cystatin C is 13-kDa protein synthesized at a constant rate in all nucleated cells. It is freely filtered by the glomerulus and is reabsorbed and catabolized completely in the proximal tubule with a lack of tubular secretion. It is considered to be a better marker of early kidney dysfunction and more reliable marker of kidney function than serum creatinine. Cystatin C is very useful biomarker in CKD and used for CVD assessment. Cystatin C seems to be better predictor of mortality and CV events than serum creatinine [87]. High cystatin C concentrations predict substantial increased risks of all-cause mortality, CV events and incident heart failure [88] and are associated with increased LVM and a concentric LVH phenotype independent of renal function [89].

Across the CVD spectrum, including peripheral arterial disease, stroke, abdominal aortic aneurysm, heart failure and coronary artery disease, a connection has been established between high plasma levels of cystatin C and negative outcomes and risk stratification, without any particular explanations behind the mechanisms of the connection. Possible ties between negative CV outcomes and high cystatin C levels could stem from deteriorated renal function, atherogenesis and inflammatory mediators, myocardial tissue remodeling as well as other factors such as genetic determinants, age and aging and social habits [90].

NGAL is 25-kDa protein with 178 amino acids belonging to the lipocalin family [91]. It is highly expressed in kidney following ischemic and nephrotoxic injury. Plasma/serum and urine NGAL is used as an early marker of acute kidney injury (AKI) in several renal diseases. NGAL has also been investigated as a prognostic marker in CKD patients. Plasma and urine NGAL levels predict progression of CKD and reflected the severity of renal disease in the study performed by Bolignano et al. [92]. However, although urine NGAL was an independent risk factor for progression among patients with established CKD of diverse etiology in Chronic Renal Insufficiency Cohort (CRIC) study, it did not substantially improve prediction of outcome events in this patient population [93]. Nevertheless, NGAL has also shown promising results as a marker of CV risk in dialysis patients. In the study by Furuya et al., elevated levels of serum NGAL were independent risk factors for de novo CVD in HD patients [94]. Furthermore, hemodialysis patients with high NGAL levels in combination with high BNP levels had the greatest risk of CVD [86].

KIM-1 is a transmembrane glycoprotein with immunoglobulin-like features. Within 24–48 h after kidney injury, KIM-1 expression is dramatically increased in proximal tubular epithelial cells. It is increased in the urine in AKI. Experimental studies suggest that KIM-1 may be an indicator of AKI to CKD transition. In the setting of patients with CHF, urinary KIM-1 outperformed NGAL and NAG in predicting a combined CV outcome of death, heart transplantation, MI, coronary angioplasty or heart failure hospitalization. However, when compared to patients with heart failure without CKD, urinary KIM-1 levels were not statistically elevated in heart failure patients with CKD [95, 96].

NAG is an enzyme of hydrolase class that is abundant in the kidney, predominantly in the lysosomes of proximal tubular cells. The increased excretion of NAG is thought to be a specific marker of functional tubular impairment in many renal pathologies. Likewise KIM-1, NAG has been a useful marker of acute kidney injury (AKI) [97]. A recent study in type 1 diabetes mellitus found that lower levels of urinary NAG were associated with the regression of microalbuminuria [98]. It has not been assessed longitudinally in CKD [95]. In patients with CHF, urinary NAG was associated with an increased risk of death, heart failure hospitalizations and heart transplantation, independent of GFR [99].

IL-18 is a proinflammatory cytokine that is released by the epithelial cells of the proximal tubule within hours of renal injury. It is significantly increased in AKI in comparison to urinary tract infection and nephrotic syndrome [96]. The destabilization of human coronary plaques can be connected to IL-18, which was originally thought to be a factor that promotes interferon- γ synthesis. In addition, in one study it was confirmed that young and middle-aged patients with a recent AMI have higher IL-18 concentration in serum than age- and sex-matched control subjects, showing that concentration of this cytokine is associated with severity of coronary atherosclerosis [100]. In addition, recent evidence suggests that serum IL-18 is an important indicator and predictor of CV death in two-year follow-up among non-diabetic patients suffering from CKD, with history of AMI in the previous year [101].

Fibroblast growth factor-23 (FGF23) is a newly discovered hormone produced in the bone that regulates phosphate and vitamin D metabolism by the kidneys. The main physiological functions of FGF23 are mediated by FGF receptors, generally in the presence of Klotho coreceptors. Decreased phosphorus excretion triggers FGF23 production, which in turn stimulates Klotho coreceptors in the kidneys [102]. CKD progression leads to compensatory elevation of FGF23 levels, resulting in typical CKD manifestations such as hyperphosphatemia, secondary hyperparathyroidism and bone disease, and progression to ESRD [80]. Elevated FGF23 has been associated with LVH, and it has been suggested that FGF23 may induce myocardial hypertrophy through a direct effect on cardiac myocytes [102]. FGF-23 has been independently associated with risk of all-cause death in dialysis and CKD patients, heart failure, CV events and death in the general population [86].

Matrix metalloproteinases (MMPs) are a large family of endopeptidases capable of degrading all components of the extracellular matrix and are therefore responsible for controlling the pathophysiological remodeling of tissues, including CV and renal systems. MMPs are classified according to their structure and substrate specificity, so MMP-2 and MMP-9 belong to the family of gelatinases that can cleave denatured collagen (gelatin), elastin and type IV collagen. Traditionally, MMPs were conceived of as exclusively anti-fibrotic tissue components; however, in the last few years, new paradigms have emerged in which inadequate extracellular matrix turnover governed by MMPs is also the hallmark of many pathological and generalized states such as inflammation, deleterious remodeling, oxidative stress and apoptosis [103]. Previous studies have demonstrated that increase in circulating levels of MMP-2 or MMP-9 are associated with arterial stiffness, hypertension and kidney disease progression in diabetic nephropathy. Recent data have proposed an important role of MMPs as markers of deleterious remodeling in the progression of renal disease and CVD [104]. Deleterious remodeling at the glomerular basement membrane, governed by pathological MMP activity, could contribute to

glomerular hyperfiltration, albuminuria and loss of renal function [103]. The vascular changes observed in CKD patients not only consist of atherosclerosis but also arteriosclerosis associated with both medial and intimal vascular calcifications. The degree of arterial stiffening and the extent of calcification are closely related, and both of these variables are strong and independent prognostic markers of all-cause and CV mortality in patients on HD. Over the last few years, matrix metalloproteinases (MMPs) have been increasingly implicated in connective tissue remodeling during atherogenesis. MMPs are involved in plaque rupture, which is the main pathological cause of myocardial infarction. Interstitial collagenase (MMP-1) is the only MMP that can cleave native collagen types I and III, which are major structural components of the fibrous plaque cap. MMP-1 might play a significant role in fibrous plaque disruption by contributing to the degradation of interstitial collagens and thinning of the fibrous cap [105].

7. Strategies to improve cardiovascular outcome in CKD

7.1. Medical therapies to improve cardiovascular outcome

Risk modification is very important in CKD patient in order to improve outcomes. Strategies to reduce CV risk in CKD patients should target traditional, nontraditional and uremia-related factors. Recent opinions suggest a potential benefit from a more individualized perspective, that takes into account patient-specific trends and distinctive dynamic features of the actual clinical situation [106].

Blood pressure management has been advocated for both reducing cardiovascular risk and for slowing the renal progression of CKD. In all CKD patients, blood pressure should be <140/90 mm Hg and in patients with CKD and diabetes or those with significant proteinuria, target values should be <130/80 mm Hg. Agents acting via the RAAS, including ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), are often recommended as first-line treatment particularly in patients with diabetes and/or proteinuria. ACEIs have positive effects on neurohormonal activity and ventricular remodeling, while ARBs seem to reduce oxidative stress and inflammation [107]. In a randomized trial performed on ESKD patients, fosinopril was found to reduce CV death, heart failure, myocardial infarction and nonfatal stroke. Beta-blockers were found to reduce the cardiac risk in coronary artery disease patients with or without CKD in the Bezafibrate Infarction Prevention study. A significant reduction of CV mortality and occurrence of sudden death was demonstrated in dialysis patients treated with carvedilol. However, new dialysis patients not previously treated with beta-blockers were more likely to develop new-onset heart failure [107].

One most neglected aspect is the effect of sodium intake on blood pressure. Only a minority of renal patients reduce sodium chloride intake to the recommended target of 7 g/day. Apart from reduced salt intake, co-administration of diuretics is mandatory (in early stages, mostly thiazides). Loop diuretics are required in advanced stages of CKD.

Anemia is considered to be one of the most important factors along with hypertension for the development of LVH in CKD patients. In terms of erythropoiesis-stimulating agents, despite

a strong suggestion of benefit to anemia management in observational studies, a number of studies in predialysis patients yielded disappointing results. The TREAT study involved diabetic CKD patients with moderate anemia treated with darbepoetin alfa [108]. Correction of anemia to hemoglobin level of 13 g/dL was associated with increased risk of stroke. Recent systematization and meta-analysis of erythropoiesis-stimulating agent therapy showed that this type of therapy has 1.5 times higher risk of stroke, as well as promotes hypertension and even increases the mortality risk, risk of severe CV events and ESRD with higher hemoglobin targets [109]. These studies have not been in vain, as they have led to changes in the usage of the medication for the purpose of correction of anemia in CKD patients to a target quantity of 11–12 g/dL [107]. Increased homocysteine has been associated with adverse CV outcomes CKD population. Folic acid, vitamin B6 and vitamin B12 in combination are an effective and inexpensive strategy to decrease homocysteine in most populations. However, trials of multivitamins in ESRD patients have been disappointing with negative results from a number of well-conducted clinical trials. This could be explained partly by the fact that vitamins fail to normalize homocysteine in ESRD patients, and toxicity from the vitamins themselves potentially could offset any theoretical benefit [110].

CKD-mineral and bone disorder (CKD-MBD) has been linked to the progression of cardiac disease, and investigators have shown a link between even mild degrees of renal injury and vascular calcification. Therefore, strategies to control phosphate, control PTH and vitamin D analogs have been mainstays of therapy in this regard [111]. In terms of phosphate binding, a Cochrane systematic review discovered that the effect of sevelamer hydrochloride and lanthanum carbonate were not as beneficial as calcium salts for the purpose of phosphate control. Some of the studies appeared to show improvements in the surrogate outcome of vascular calcification, which subsequently did not add to any reduction in CV morbidity or mortality [111].

Statins play a central role in the primary and secondary management of the CVD risk. Results of SHARP (Study of Heart and Renal Protection) study showed a significant benefit of the combination of simvastatin and ezetimibe in lowering the risk of major atherosclerotic events. This study included both ESRD patients and CKD patients not on dialysis. However, the subgroup of ESRD patients in SHARP seemed to experience less benefit compared to lesser degrees of CKD, and all-cause mortality was unaffected. Consistent with this negative findings, the initiation of treatment with rosuvastatin in the AURORA study had no significant effect on the composite primary end point of death from CV causes, nonfatal MI or nonfatal stroke in ESRD patient undergoing HD. It seems that CKD patients could benefit from statins but pragmatic approach is to recommend therapy with statins in CKD stages I–IV with increased risk of CVD [107].

7.2. Dialytic strategies to improve cardiovascular outcome

Dialytic strategies are used to improve cardiovascular outcome. Dialysis technology improvements should lead to improvements in hemodynamic stability, oxidative and inflammatory stress and increase the efficiency of removing low and middle toxins, which leads to ‘cardioprotective dialysis’. Both the use of modern machines that fit safety, quality of therapy,

performance and monitoring standards and the use of new biomaterials designed to mitigate inflammation and enhance membrane performance represent the application of new technologies [81]. In HD synthetic membranes are regarded as being more “biocompatible” in that they incite less of an immune response than cellulose-based membranes. However, Cochrane meta-analysis found no evidence of benefit when synthetic (high-flux) membranes were compared to cellulose/modified cellulose membranes in terms of reduced mortality in HD patients. This meta-analysis also showed that synthetic membranes achieved significantly higher Kt/V values when compared to modified cellulose membranes [112]. Results that are shown in the study of House et al. were compared the use of high-flux and low-flux hemodialysis on homocysteine and lipid profiles. The larger intradialytic effect of high-flux dialysis on homocysteine did not significantly affect predialysis levels after 3 months of study [113]. In contrast to this finding, high-flux membranes were associated with improved 2-year survival in the study of Chauveau et al. [114]. Other authors have reported that ‘hemofiltration’ or ‘hemodiafiltration’ treatment was associated with better blood pressure control, lower incidence of intradialytic hypotension or arrhythmia, better β 2-microglobulin, phosphate clearance, reduced inflammation and oxidative stress as well as reduced hospitalization rate [81]. Ultrapure dialysate might also contribute to improvements in the morbidity and mortality of HD patients. Honda et al. found that serum myeloperoxidase and hs-CRP levels were significantly decreased in the patients treated with ultrapure dialysate compared to the patients undergoing HD using conventional dialysate. Ultrapure dialysate can improve the chronic inflammatory status, oxidative stress, and lipid abnormalities, suggesting a possible contribution to reduced CVD risk [115].

PD might circumvent the hemodynamic instability of frequent and rapid ultrafiltration associated with conventional HD. Previous randomized controlled trials and many other observational studies have produced conflicting results as to which therapy may have a CV advantage. Some registry data suggests PD is associated with a lower mortality than HD in the first 1–2 years but thereafter may be higher on PD than HD. Other registry data do not support this. The decision to undergo either PD or HD is based on many factors which include the differential damage the RRT may have on the CV system [116].

8. Post-translational modifications (PTMs) in CKD and CVD

Post-translational modifications (PTMs) of proteins and peptides have recently gained much attention, as they are involved in the pathogenesis of CVD and also play a role in the progression of CKD. PTMs are covalent changes of proteins or peptides that are altered either by proteolytic cleavage or by adding moieties to one or more amino acids. The most commonly reported PTMs are carbamylation, glycation and oxidation [117].

8.1. Carbamylation

Carbamylation is a nonenzymatic spontaneous reaction of a primary amine or a free sulfhydryl group of proteins with isocyanate. This process is increased during CKD because of hyperuricemia, and in other pathologies like atherosclerosis, where isocyanic may be formed

from thiocyanate by myeloperoxidase in atheroma plates [118]. As kidney function declines, metabolic substances such as urea and its derivatives, cyanate and ammonia, dramatically increase thus leading to a significant amount of carbamylated proteins. Carbamylation of caeruloplasmin increases oxidative stress by decreasing the ferroxidase activity; carbamylated HDL reduces the lecithin-cholesterol acyltransferase thus inducing cholesterol accumulation; carbamylated LDL induces endothelial apoptosis and proliferation [76]. Amino acid therapy is applicable for reduction of protein carbonylation in CKD patients. The United States Food and Drug Administration (FDA) recently approved intravenous amino acid solution for this purpose (clinical trials.gov Identifier: NCT01612429). It was reported that uremic patients are deficient of free amino acids so that an infusion of free amino acids protects the proteins from carbamoylation due to the fact that both free amino acids and proteins compete with cyanate [117].

8.2. Glycation

Glycation is a nonenzymatic reaction of reducing sugars with the amino group of amino acids, nucleic acids, lipids and proteins. AGEs are considered extremely significant in determining the development of CVD in diabetic patients by changing the structure, function and characteristics of tissue through crosslinking inter- and extracellular matrix proteins and modulation of cellular processes through binding to receptors located on the cell's surface [119]. As CKD develops, the kidney is unable to successfully excrete AGE, leading to high concentrations. AGEs can be considered as uremic toxins, as they increase CV morbidity in patients suffering from CKD by altering their vascular matrix, thus increasing arterial stiffening, vascular calcifications and left ventricular hypertrophy. The pathophysiological effects of AGEs can be blocked by using inhibitors of AGE synthesis (aminoguanidine, pyridoxamine, benfotiamine, ALT-946, OBP-9195 and pimaginedine); AGE cross-link breakers (alagebrium, N-phenacetyl thiazolium, TRC4186 and C-36) and anti-RAGE, which serve as a receptor blocker [120].

8.3. Oxidation/carbonylation

Oxidation generally refers to the loss of electrons or gain of oxygen or loss of hydrogen by a molecule. The addition of reactive carbonyl functional groups on proteins is generally termed as protein carbonylation. Oxidation mechanism is also involved in carbonylation. There is a close relationship between oxidative stress and carbonyl stress and these are enhanced in correlation with the progression of CKD among predialysis CKD patients. Proteins are the major targets for these reactive oxygen and nitrogen species, leading to peptide-bound cleavage or oxidation of side chains of amino acids resulting in the structural and functional changes of oxidized proteins. Almost all amino acids are vulnerable to radical attacks of reactive oxygen and nitrogen species. Oxidized forms of phenylalanine and tyrosine, markers for the oxidative damage, are all together termed as advanced oxidation protein products (AOPP). Clinical studies revealed that LDL oxidation, AOPP and protein carbonyls can be used as biomarkers of oxidative stress in CKD patients. AOPP levels independently predict atherosclerotic CV events in patients with CKD in the predialysis phase and might directly contribute to the uremia-associated accelerated atherogenesis [117]. Oxidized LDL could be involved in

the stiffening of vascular wall which contributes to structural changes in the artery that may lead to CVD [121]. Anti-oxidant therapy could be beneficial in uremic patients with oxidative stress since the oxidative metabolites accumulate in CKD. Treatment with N-acetylcysteine in dialysis patients reduced the levels of oxidized LDL and partly improved anemia [122]. Vitamin E and C as well as ACEIs reduce ROS production, thereby decreasing oxidative stress in CKD patients [123]. Coenzyme Q10 (CoQ10) administration was effective in protecting against oxidative stress in dialysis patients in a phase IV clinical trial (ClinicalTrials.gov Identifier: NCT00307996).

Author details

Damir Rebić* and Aida Hamzić-Mehmedbašić†

*Address all correspondence to: damir.rebic@gmail.com

Clinic for Nephrology, Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina

†Contributed equally to the paper.

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